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Comparative Effectiveness of Natalizumab, Fingolimod, and Injectable Therapies in Pediatric-Onset Multiple Sclerosis

A Registry-Based Study

Tim Spelman, PhD, MBBS, BSc, Gabrielle Simoneau, PhD, MSci, BSc, Robert Hyde, PhD, BSc, Robert Kuhelj, PhD, Raed Alroughani, MD, Serkan Ozakbas, MD, Rana Karabudak, MD, Bassem I. Yamout, MD, Samia J. Khoury, MD, Murat Terzi, MD, Cavit Boz, MD, Dana Horakova, MD, PhD, Eva Kubala Havrdova, MD, PhD, Bianca Weinstock-Guttman, MD, Francesco Patti, MD, Ayse Altintas, MD, Saloua Mrabet, MD, Riadh Gouider, MD, Jihad Inshasi, MD, Vahid Shaygannejad, PhD, Sara Eichau, MD, PhD, W. Luke Ward, BCS, and Helmut Butzkueven, MBBS, PhD, for the MSBase Investigators

Correspondence
Dr. Spelman
tim@burnet.edu.au

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Abstract

Background and Objectives

Patients with pediatric-onset multiple sclerosis (POMS) typically experience higher levels of inflammation with more frequent relapses, and though patients with POMS usually recover from relapses better than adults, patients with POMS reach irreversible disability at a younger age than adult-onset patients. There have been few randomized, placebo-controlled clinical trials of multiple sclerosis (MS) disease-modifying therapies (DMTs) in patients with POMS, and most available data are based on observational studies of off-label use of DMTs approved for adults. We assessed the effectiveness of natalizumab compared with fingolimod using injectable platform therapies as a reference in pediatric patients in the global MSBase registry.

Methods

This retrospective study included patients with POMS who initiated treatment with an injectable DMT, natalizumab, or fingolimod between January 1, 2006, and May 3, 2021. Patients were matched using inverse probability treatment weighting. The primary outcome was time to first relapse from index therapy initiation. Secondary study outcomes included annualized relapse rate; proportions of relapse-free patients at 1, 2, and 5 years; time to treatment discontinuation; and times to 24-week confirmed disability worsening and confirmed disability improvement.

Results

A total of 1,218 patients with POMS were included in this analysis. Patients treated with fingolimod had a significantly lower risk of relapse than patients treated with injectable DMTs (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.29–0.83; $p = 0.008$). After adjustment for prior DMT experience in the unmatched sample, patients treated with natalizumab had a significantly lower risk of relapse than patients treated either with injectable DMTs (HR, 0.15;

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From the MSBase Foundation (T.S.), Melbourne, Australia; Department of Clinical Neuroscience (T.S.), Karolinska Institute, Stockholm, Sweden; Biogen (G.S.), Toronto, Ontario, Canada; Biogen (R.H., Robert Kuhelj), Baar, Switzerland; Division of Neurology (R.A.), Department of Medicine, Amiri Hospital, Sharq, Kuwait; Dokuz Eylul University (S.O.), Konak/Izmir; Hacettepe University (Rana Karabudak), Ankara, Turkey; Nehme and Therese Tohme Multiple Sclerosis Center (B.I.Y., S.J.K.), American University of Beirut Medical Center, Lebanon; 19 Mayis University (M.T.), Samsun; KTU Medical Faculty Farabi Hospital (C.B.), Trabzon, Turkey; Department of Neurology and Center of Clinical Neuroscience (D.H., E.K.H.), First Faculty of Medicine, Charles University in Prague and General University Hospital, Czech Republic; Department of Neurology (B.W.-G.), Buffalo General Medical Center, Buffalo, NY; Department of Medical and Surgical Sciences and Advanced Technologies (F.P.), GF Ingrassia, Catania, Italy; Department of Neurology (A.A.), School of Medicine and Koc University Research Center for Translational Medicine (KUTTAM), Koc University, Istanbul, Turkey; Department of Neurology and Clinical Investigation Center Neurosciences and Mental Health (S.M.), Razi University Hospital; Department of Neurology (R.G.), Razi University Hospital, Tunis, Tunisia; Rashid Hospital (J.I.), Dubai, United Arab Emirates; Isfahan University of Medical Sciences (V.S.), Iran; Department of Neurology (S.E.), Hospital Universitario Virgen Macarena, Sevilla, Spain; Ashfield MedComms (W.L.W.), Middletown, CT; Department of Neuroscience (H.B.), Central Clinical School, Monash University, Melbourne; and Department of Neurology (H.B.), Box Hill Hospital, Monash University, Box Hill, Victoria, Australia.

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Glossary

AOMS = adult-onset MS; **ARR** = annualized relapse rate; **CDI** = confirmed disability improvement; **CDW** = confirmed disability worsening; **CI** = confidence interval; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IPTW** = inverse probability of treatment weighting; **MS** = multiple sclerosis; **POMS** = pediatric-onset multiple sclerosis; **PS** = propensity score; **RMS** = relapsing MS; **RR** = risk ratio.

95% CI 0.07–0.31; $p < 0.001$) or fingolimod (HR, 0.37; 95% CI 0.14–1.00; $p = 0.049$). The adjusted secondary study outcomes were generally consistent with the primary outcome or with previous observations. The findings in the inverse probability treatment weighting–adjusted patient populations were confirmed in multiple sensitivity analyses.

Discussion

Our analyses of relapse risk suggest that natalizumab is more effective than fingolimod in the control of relapses in this population with high rates of new inflammatory activity, consistent with previous studies of natalizumab and fingolimod in adult-onset patients and POMS. In addition, both fingolimod and natalizumab were more effective than first-line injectable therapies.

Classification of Evidence

This study provides Class II evidence that patients with POMS treated with natalizumab had a lower risk of relapse than those with fingolimod.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system, with an estimated worldwide prevalence in 2020 of more than 2.8 million cases.[1] Although symptoms of MS usually first appear in adults between age 20 and 50 years,[2] approximately 3%–5% of MS cases are of pediatric onset, with first symptoms in childhood or, more commonly, in adolescence.[3-5]

Patients with pediatric-onset MS (POMS) typically experience higher levels of inflammation with more frequent relapses than patients with adult-onset MS (AOMS).[6-8] Although pediatric patients take longer than adults to reach irreversible disability, this point still occurs at a younger age.[9] A study of 394 patients with POMS found that patients exhibited a median time of 28.9 years to reach an Expanded Disability Status Scale (EDSS) score of 6, when the median age of patients was 42.2 years, approximately 10 years younger than the average age to EDSS 6 for AOMS.[9] In addition, patients with POMS generally have poorer cognitive performance and long-term socioeconomic outcomes than do patients diagnosed with AOMS or healthy controls, probably because brain inflammation can interfere with ongoing cerebral maturation processes in adolescence.[10,11] Early intervention with an appropriate efficacious disease-modifying therapy (DMT) is therefore essential for reducing the risk of persistent long-term disability in these patients.[12]

There have been few randomized, placebo-controlled clinical trials of MS DMTs in pediatric patients with POMS, and therefore, many of the available data are based on observational studies of off-label use of DMTs approved for adults.[13] Patients with pediatric-onset and adult-onset MS share similar genetic and environmental risk factors, suggesting similar pathophysiology, and therefore, pediatric patients typically show similar responses to DMTs.[14,15] The most widely used first-line therapies in patients with POMS have been injectable DMTs, including interferon-β and glatiramer acetate.[16] However, these first-line agents may be poorly tolerated or fail to provide adequate control of disease activity,[17] prompting the need to escalate therapy to more efficacious DMTs.[18]

Fingolimod was approved in the United States and the European Union for pediatric patients with MS in 2018, on the basis of the randomized clinical trial of fingolimod vs interferon beta-1a in pediatric patients with MS.[19-21] Observational studies of pediatric patients with MS have reported effectiveness of other DMTs as well, including dimethyl fumarate and natalizumab.[13,22-28]

Comparative effectiveness data in patients with POMS are also limited. In the absence of comparative data from head-to-head randomized clinical trials, observational studies can provide useful information for treatment decision making. The primary research question being addressed by this study is: what is the effectiveness of natalizumab compared with fingolimod and with reference to the injectable platform therapies (subcutaneous [SC] interferon beta-1b, intramuscular [IM] or SC interferon beta-1a, IM or SC peginterferon beta-1a, or SC glatiramer acetate) in patients with POMS in the global MSBase registry?[29]

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase registry consists of anonymized patient-level data from contributing member sites.[30] Institutional review

board and ethics committee approvals were required for initiation of each site according to applicable local laws and regulations. Written informed consent was obtained for each patient before their inclusion in the database in accordance with the Declaration of Helsinki.

Study Design and Sample

This was a retrospective cohort study based on MSBase registry data from 100 centers and 32 countries. Patients diagnosed with POMS who initiated treatment with an injectable DMT, natalizumab, or fingolimod between January 1, 2006, and May 3, 2021, were included so as to have a contemporary sample since the availability of the second generation of MS treatments. Data were collected from 2006, when natalizumab first became available, through 2021. A sensitivity analysis was performed using data as of 2010, when fingolimod became available for use.

Inclusion and Exclusion Criteria

Eligible patients had a diagnosis of pediatric-onset relapsing MS (RMS) and initiated index therapy treatment before age 18 years. Patients had to be naïve to prior therapy or to have switched from an injectable DMT. Patients who initiated treatment with an injectable DMT and who switched to either natalizumab or fingolimod during the follow-up period were assigned to the natalizumab or fingolimod cohort, respectively. Exclusion criteria included prior treatment with natalizumab, fingolimod, cladribine, rituximab, ocrelizumab, alemtuzumab, dimethyl fumarate, or teriflunomide, or prior treatment with a recognized immunosuppressive agent, such as azathioprine, methotrexate, cyclophosphamide, or mitoxantrone.

Patient Cohorts

Patients were assigned to 1 of 3 cohorts on the basis of their index therapy: injectable DMT, natalizumab, or fingolimod. Patients contributed to a cohort from baseline (therapy initiation) until the patient discontinued the therapy or until the end of the follow-up.

Outcomes and Assessments

Primary Outcome

The primary outcome was the time to first relapse from index therapy initiation.

Secondary Outcomes

Secondary study outcomes included annualized relapse rate (ARR); proportions of patients who were relapse-free at 1, 2, and 5 years postbaseline; time to treatment discontinuation; and times to 24-week confirmed disability worsening (CDW) and 24-week confirmed disability improvement (CDI) in Expanded Disability Status Scale (EDSS) scores. ARR was calculated during the entire duration of follow-up. Relapses were defined as new or recurrent neurologic symptoms occurring >30 days after the onset of a previous relapse. Symptoms occurring ≤30 days after a previous relapse were counted only as 1 relapse, and the onset date used in the analysis was the onset date of the first relapse. Time to treatment discontinuation was calculated during the entire duration of follow-up time. Time to 24-week CDW or 24-week CDI was calculated from baseline until disease progression or improvement, respectively. CDW was defined as a confirmed increase of ≥0.5 point in EDSS score for patients with a baseline EDSS score >5.5; ≥1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive; and ≥1.5 points for those with a baseline EDSS score of 0. For the confirmation of disability worsening, EDSS scores recorded within 30 days after the onset of a relapse were excluded. Initial and confirmatory disability progression had to be assessed on consecutive visits. CDI was defined as a confirmed decrease in EDSS score of ≥1 point for patients with a baseline EDSS score ≥2.0. CDI was not calculated for patients with a baseline EDSS score <2.0. For the confirmation of disability improvement, EDSS scores recorded within 30 days after the onset of a relapse were excluded. Initial and confirmatory disability improvement had to be assessed on consecutive visits.

Statistical Analyses

Analysis Populations

All patients fulfilling all the inclusion criteria and not meeting any of the exclusion criteria were included in the analysis population. A multinomial logistic regression model was used to calculate propensity scores (PSs), and inverse probability of treatment weighting (IPTW) was used to balance groups by baseline patient characteristics (age, sex, disease duration, baseline EDSS, country, prior DMT, relapse count in the past year and past 2 years, MRI lesion count, and presence of gadolinium-enhanced [Gd+] lesions). Index calendar year was not included as a covariate to avoid positivity violation issues during modeling. This enabled a broader analysis that included patients enrolled before the availability of some treatments in their country.

Outcome Assessments

For the primary and secondary outcome assessments, average treatment-effect weights—which may be interpreted as targeting a combined population of patients treated with natalizumab, fingolimod, or injectable platform therapies—for each of the 3 treatment cohorts were estimated. Outcomes were assessed separately for pairwise treatment comparison. For the primary outcome, the adjusted cumulative probability of relapse postbaseline was estimated using a weighted Cox proportional hazard model controlling for treatment arm, with adjustment for previous DMT use (naïve vs experienced), count of prebaseline DMTs, and index year. Specifically, a time-to-first-event (i.e., time to first relapse) Cox model was used to quantify the relative hazard or risk of first relapse in one treatment compared with a comparator treatment group. The secondary ARR endpoint was estimated using a weighted negative binomial regression model controlling for treatment arm, with an offset for log-transformed follow-up time. Proportions of relapse-free patients were evaluated using a weighted logistic regression model controlling for the treatment arm. Secondary time-to-event analyses were performed

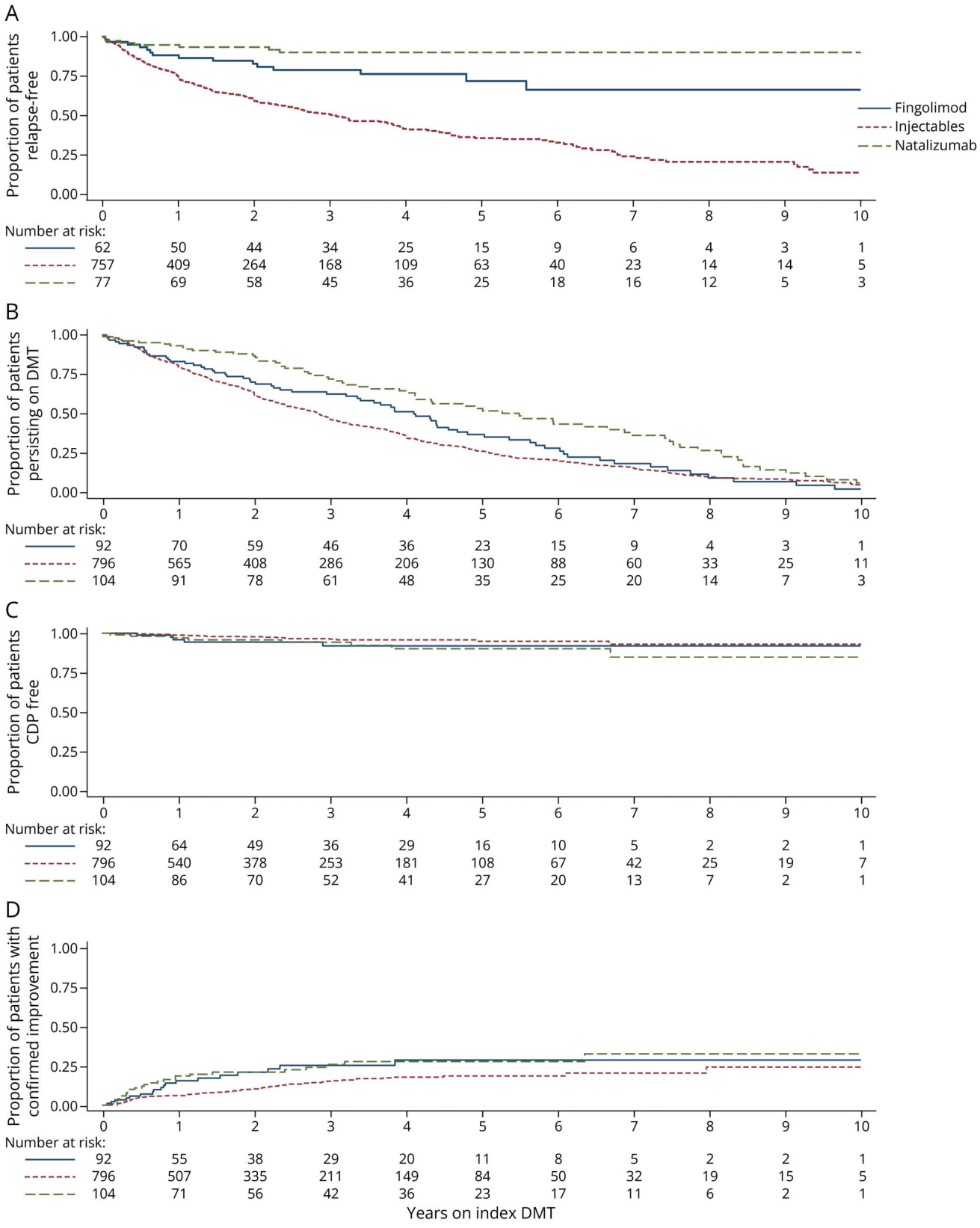
Table 1 Baseline Characteristics for Patients With Pediatric-Onset RMS

Characteristic	Natalizumab[a] (n = 111)	Fingolimod[b] (n = 104)	Injectable DMT[c] (n = 1,003)	Standardized difference, unweighted			Standardized difference, weighted		
				Natalizumab vs fingolimod	Natalizumab vs injectables	Fingolimod vs injectables	Natalizumab vs fingolimod	Natalizumab vs injectables	Fingolimod vs injectables
Age, mean (SD), y	15.80 (2.28)	16.00 (2.89)	16.06 (1.98)	0.000	0.000	−0.027	0.000	0.008	−0.008
Female, n (%)	83 (74.8)	75 (72.1)	721 (71.9)	0.060	0.065	0.005	0.047	0.063	0.049
Country, n (%)									
Australia	14 (12.6)	21 (20.2)	63 (6.3)	0.214	−0.166	−0.279	0.194	−0.071	−0.250
Italy	10 (9.0)	2 (1.9)	68 (6.8)						
Kuwait	32 (28.8)	11 (10.6)	74 (7.4)						
Spain	9 (8.1)	14 (13.5)	51 (5.1)						
Turkey	5 (4.5)	25 (24.0)	282 (28.1)						
Czech Republic	5 (4.5)	2 (1.9)	39 (3.9)						
Iran	0 (0.0)	0 (0.0)	46 (4.6)						
Belgium	3 (2.7)	3 (2.9)	29 (2.9)						
Canada	5 (4.5)	1 (1.0)	24 (2.4)						
Other	28 (25.2)	25 (24.0)	327 (32.6)						
MS duration, mean (SD), y	1.74 (1.71)	1.91 (1.75)	1.32 (1.65)	−0.096	0.248	0.343	−0.016	0.031	0.148
BL EDSS score,[d] median (IQR)	1.5 (1, 2.5)	1 (0, 2)	1.5 (1, 2.5)	0.292	0.130	−0.161	0.155	0.063	−0.137
Prior DMT use, n (%)									
Naïve	64 (57.7)	48 (46.2)	865 (86.2)	0.231	−0.669	−0.932	0.135	−0.265	−0.420
Experienced	47 (42.3)	56 (53.9)	138 (13.8)						
Number of prior DMTs, mean (SD)	0.60 (0.83)	0.69 (0.80)	0.15 (0.39)	−0.108	0.699	0.864	−0.009	0.216	0.341
Relapses in year before BL, mean (SD)	1.53 (1.23)	1.12 (1.17)	1.07 (0.95)	0.346	0.420	0.044	0.083	0.037	−0.146
Index year, n (%)									
2006–2010	22 (19.8)	1 (1.0)	359 (35.8)	−0.397	0.421	0.881	0.076	0.514	0.519
2011–2015	49 (44.1)	59 (56.7)	433 (43.2)						
2016+	40 (36.0)	44 (42.3)	211 (21.0)						
Follow-up time, y[e]									
Mean (SD)	3.91 (2.94)	3.03 (2.79)	2.19 (2.45)	—	—	—	—	—	—
Median (IQR)	3.21 (1.59, 5.55)	2.38 (0.59, 4.73)	1.37 (0.22, 3.41)	—	—	—	—	—	—

Abbreviations: BL = baseline; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IM = intramuscular; IQR = interquartile range; MS = multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous.
[a] Patients did not have prior fingolimod treatment.
[b] Patients did not have prior natalizumab treatment.
[c] Includes IM or SC interferon beta-1a, SC interferon beta-1b, SC glatiramer acetate, and IM or SC peginterferon beta-1a.
[d] Nearest EDSS score within 6 mo of BL.
[e] Follow-up time while on index DMT.

using a weighted Cox proportional hazard model controlling for treatment arm. Errors (95% confidence intervals [CIs]) for all primary and secondary outcome analyses were calculated using robust sandwich estimation. Hazard proportionality was assessed using postestimation hazard proportionality tests combined with analysis of scaled Schoenfeld residuals.

Figure Cumulative Probabilities of (A) Remaining Relapse-Free, (B) Remaining on Index DMT, (C) Remaining Free of 24-Week CDW for Patients Treated With Natalizumab, Fingolimod, or Injectable Therapies, and (D) Reaching 24-Week CDI for Patients Treated With Natalizumab, Fingolimod, or Injectable Therapies



CDI = confirmed disability improvement; CDW = confirmed disability worsening; DMT = disease-modifying therapy.

Table 2 PS-IPTW Adjusted Kaplan-Meier Estimates of Time to First Relapse

Comparison	PS-IPTW adjusted HR (95% CI)[a]	*p* Value
Natalizumab vs fingolimod	0.37 (0.14–1.00)	0.049
Natalizumab vs injectable DMT	0.15 (0.07–0.31)	<0.001
Fingolimod vs injectable DMT	0.49 (0.29–0.83)	0.008

Abbreviations: CI = confidence interval; DMT = disease-modifying therapy; HR = hazard ratio; PS-IPTW = propensity score inverse probability of treatment weighting.
[a] Adjusted for prior DMT (naïve vs experienced), count of prebaseline DMTs, and index year.

Sensitivity Analyses

Five sensitivity analyses were conducted to assess the validity of assumptions and robustness of the results (eSAP 1, links.lww.com/WNL/D452). For the PS–matching analysis, patients were matched 1:1 with replacements using PSs instead of IPTW. A weight-trimming analysis was performed to assess the effect of removing outlier PS weights by removing the first quartile of scores from the natalizumab-treated, fingolimod-treated, and injectable DMT–treated groups. For the alternative weighting analyses, the outcome analyses were repeated using average treatment effect among the treated (ATT) weighting to produce different target populations for each treatment group or the combined (overlap) patient population. A cohort entry date analysis was performed by restricting data to patients who were treated after January 1, 2010, when fingolimod was available for use. For the MRI lesion analysis, data were restricted to patients with a baseline MRI and included number of MRI lesions and presence of Gd+ lesions as covariates in the PS model.

A sensitivity analysis was also conducted to assess the effect of index calendar year on outcomes.

Descriptive Statistics

Continuous variables were assessed using mean, standard deviation, median, 25th and 75th percentiles, or minimum and maximum, as appropriate. Categorical variables were summarized as frequencies and percentages. Descriptive statistics were tabulated for all baseline characteristics by cohort. The number of visits with an EDSS measurement after baseline was summarized separately by cohort as both a categorical and a continuous measure. The intervisit time was calculated as the time in months between consecutive visits with an EDSS measurement. The reasons for treatment discontinuation were summarized using frequency and percentage. No adjustments for multiplicity were conducted.

Missing Data

In general, missing values were not imputed. Patients with missing data in any variable required for a given analysis were not included in that analysis. Partial dates were imputed for dates of relapse events, EDSS measurements, and therapy initiation or discontinuation. Unknown days and months were imputed as the 1st and January, respectively.

Data Availability

The clinical data for this study were obtained under a license agreement with MSBase (msbase.org). However, no patient-level data were disclosed as part of the study. Therefore, all data relevant to the study are presented in this manuscript and the eMaterials. The study protocol and statistical analysis plan are available in eSAP 1 (links.lww.com/WNL/D452).

Results

Patients

As of May 3, 2021, there were 76,152 patients included in the MSBase registry, of whom 5,410 were diagnosed with POMS. Of those patients with POMS, 1,218 met the inclusion criteria: diagnosis of RMS; initiated treatment with an injectable DMT, fingolimod, or natalizumab on or after January 1, 2006; and had a baseline EDSS assessment within 6 months of the index date (Table 1). The greatest reason for exclusion of patients with POMS with RMS was not initiating treatment with DMT (at least 2 consecutive visits with no treatment reported after their first MS defining attack). Patients aged younger than 12 years represented 3.6%, 5.8%, and 4.0% of the natalizumab, fingolimod, and injectables cohorts, respectively. Although baseline age, sex, and EDSS score

Table 3 PS-IPTW Adjusted Annualized Relapse Rates

Index therapy	N	Total relapses	Follow-up years[a]	Adjusted ARR (95% CI)[b]	*p* Values		
					Natalizumab vs fingolimod	Natalizumab vs injectable DMT	Fingolimod vs injectable DMT
Injectable DMT	1,003	771	2,199.82	0.351 (0.326–0.376)			
Natalizumab	111	33	434.27	0.076 (0.052–0.107)	0.067	<0.0001	<0.0001
Fingolimod	104	37	314.91	0.118 (0.083–0.162)			

Abbreviations: ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; PS-IPTW = propensity score inverse probability of treatment weighting.
[a] Follow-up time while on index DMT.
[b] Adjusted for prior DMT (naïve vs experienced), count of prebaseline DMTs, and index year.

Table 4 PS-IPTW Adjusted Kaplan-Meier Estimates of Secondary Outcomes

Outcome	PS-IPTW adjusted HR (95% CI)[a]	*p* Value
Time to discontinuing index DMT		
Natalizumab vs fingolimod	1.00 (0.56–1.78)	0.998
Natalizumab vs injectable DMT	0.24 (0.16–0.36)	<0.001
Fingolimod vs injectable DMT	0.24 (0.15–0.39)	<0.001
Time to demonstrating 24-wk CDW		
Natalizumab vs fingolimod	0.84 (0.26–2.75)	0.782
Natalizumab vs injectable DMT	2.17 (0.81–5.85)	0.124
Fingolimod vs injectable DMT	2.27 (0.73–7.06)	0.156
Time to reaching 24-wk CDI		
Natalizumab vs fingolimod	0.97 (0.52–1.83)	0.936
Natalizumab vs injectable DMT	2.24 (1.33–3.76)	0.002
Fingolimod vs injectable DMT	2.98 (1.70–5.23)	<0.001

Abbreviations: CDI = confirmed disability improvement; CI = confidence interval; CDW = confirmed disability worsening; DMT = disease-modifying therapy; HR = hazard ratio; PS-IPTW = propensity score inverse probability of treatment weighting.
[a] Adjusted for prior DMT (naïve vs experienced), count of prebaseline DMT, and index year.

were generally similar between groups, before IPTW adjustment, 50% of covariates displayed standardized differences >0.20 (Table 1). After PS weighting, pairwise standardized differences were less than 20% for all confounders included in the derivation of the PS, with the exception of country for the fingolimod vs injectables comparison.

Patients who were prescribed injectable DMTs as the index therapy had shorter MS disease duration and fewer relapses in the past year than did those who received natalizumab or fingolimod.

Outcomes

Time to First Relapse

Kaplan-Meier estimated proportions of relapse-free patients at years 1, 2, and 5 were the greatest among those treated with natalizumab and the smallest among patients treated with an injectable DMT (Figure, A). At year 1, the proportion of relapse-free patients (95% CI) was highest for natalizumab (94.8% [86.6–98.0]), followed by fingolimod (88.2% [76.9–94.2]) and injectable DMTs (73.3% [69.7–76.6]). At year 2, the proportion of relapse-free patients (95% CI) was highest for natalizumab (93.4% [84.8–97.2]), followed by fingolimod (82.9% [70.5–90.4]) and injectable DMTs (59.8% [55.6–63.7]). At year 5, the proportion of relapse-free patients (95% CI) was highest for natalizumab (90.0% [80.1–95.1]), followed by fingolimod (71.9% [55.5–83.1]) and injectable DMTs (35.8% [30.6–40.9]).

Patients treated with natalizumab demonstrated a significantly lower risk of relapse than did patients treated with an injectable DMT (adjusted hazard ratio [HR], 0.15; 95% CI 0.07–0.31; $p < 0.001$) and a lower risk of relapse than patients treated with fingolimod (adjusted HR, 0.37; 95% CI 0.14–1.00; $p = 0.049$) (Table 2). Patients treated with fingolimod also had a significantly lower risk of relapse than those treated with injectable DMTs (adjusted HR, 0.49; 95% CI 0.29–0.83; $p = 0.008$).

Secondary Outcomes

The ARRs (95% CI) in patients treated with natalizumab (0.08 [0.05–0.11]) and in patients treated with fingolimod (0.12 [0.08–0.16]) were both significantly lower than the ARRs in patients treated with an injectable DMT (0.35 [0.33–0.38]; $p < 0.0001$ for both comparisons; Table 3). ARR was not significantly different for natalizumab-treated patients vs fingolimod-treated patients (risk ratio [RR] [95% CI]: 0.68 [0.41–1.12]; $p = 0.07$).

The time to index treatment discontinuation was significantly longer in patients treated with natalizumab or fingolimod than in patients treated with injectable DMTs (Figure, B; Table 4), as demonstrated by a lower risk of discontinuing index treatment during follow-up (adjusted HR [95% CI]: natalizumab vs injectable DMT, 0.24 [0.16–0.36]; fingolimod vs injectable DMT, 0.24 [0.15–0.39]; $p < 0.001$ for both comparisons). However, the time to discontinuation of index therapy was similar for natalizumab-treated and fingolimod-treated patients (adjusted HR, 1.00; 95% CI 0.56–1.78; $p = 0.998$).

The time to 24-week CDW was not significantly different in any treatment group; however, natalizumab and fingolimod demonstrated a nominally reduced risk of 24-week CDW in comparison with injectable DMTs (Figure, C; Table 4). Adjusted HRs for the time to 24-week CDW (95% CI) were 2.17 (0.81–5.85; $p = 0.124$) for natalizumab vs injectable DMTs and 2.27 (0.73–7.06; $p = 0.156$) for fingolimod vs injectable DMTs.

The cumulative proportion of patients demonstrating 24-week CDI was significantly greater in patients treated with either natalizumab or fingolimod than in patients treated with injectable DMTs (Figure, D; Table 4). Adjusted HRs (95% CI) for time to 24-week CDI were 2.24 (1.33–3.76; $p = 0.002$) for natalizumab vs injectable DMTs and 2.98 (1.70–5.23; $p < 0.001$) for fingolimod vs injectable DMTs.

Reasons for Index Treatment Discontinuation

Treatment discontinuations occurred among 709, 76, and 72 patients treated with injectable DMTs, fingolimod, and natalizumab, respectively. Within each treatment group, the most common reported reason for treatment discontinuation was lack of improvement (fingolimod, 29.0%; injectable DMTs, 22.6%; natalizumab, 22.2%). The reason for discontinuation was not reported for approximately a third of patients (injectable DMTs, 33.9%; natalizumab, 33.3%; fingolimod, 27.6%).

For patients with available data, natalizumab patients most often switched to fingolimod as their next DMT (n = 9 of 35), fingolimod patients most often switched to natalizumab (n = 12 of 36), and patients initiating an injectable DMT most often switched to another injectable platform (n = 289 of 660) (eTable 1, links.lww.com/WNL/D451).

Description of Monitoring Times

Postbaseline visits with an EDSS measurement (mean [SD]) were more common among patients treated with natalizumab (5.9 [7.6]) or fingolimod (4.3 [5.8]) than with an injectable DMT (2.0 [3.9]). However, the intervisit time (mean months between visits with an EDSS evaluation [SD]) was similar between treatment groups (natalizumab, 5.7 [4.9]; fingolimod, 5.0 [3.9]; injectable DMTs, 5.3 [4.9]), indicating that visits were conducted at a consistent rate regardless of treatment in patients for whom EDSS was evaluated.

Sensitivity Analyses

Analyses of 1:1 PS–matched patients (n = 54 patients in each treatment group) produced similar results to the main IPTW analyses (eTables 2–4, links.lww.com/WNL/D451). The time to first relapse was nominally reduced in matched patients treated with natalizumab or fingolimod in comparison with injectable DMTs, as evidenced by a lower risk of relapse during follow-up (HR [95% CI]: natalizumab vs injectable DMTs: 0.44 [0.19–1.02], $p = 0.055$; fingolimod vs injectable DMTs: 0.48 [0.21–1.11], $p = 0.085$). ARR (95% CI) was significantly reduced in PS–matched patients treated with natalizumab (0.07 [0.04–0.11]) or fingolimod (0.08 [0.05–0.14]) in comparison with injectable DMTs (0.42 [0.27–0.62]) ($p < 0.001$ for both comparisons). The time to index treatment discontinuation was significantly longer in matched patients treated with natalizumab or fingolimod than with injectable DMTs and was demonstrated by a reduced risk of discontinuing index treatment during follow-up (HR [95% CI]: natalizumab vs injectable DMTs, 0.18 [0.10–0.35]; fingolimod vs injectable DMTs, 0.28 [0.15–0.52]; $p < 0.001$ for both comparisons). As in the primary analysis, time to 24-week CDW was not significantly different in any treatment group. Time to 24-week CDI was also similar to that in the primary analysis, with a significantly improved time to CDI observed with fingolimod vs injectable DMTs (HR, 8.22; 95% CI 1.07–62.92; $p = 0.043$) and nominally improved time to CDI in patients treated with natalizumab vs injectable DMT (HR, 5.63; 95% CI 0.72–43.92; $p = 0.099$).

The results from other sensitivity analyses were also consistent with the primary analysis. A trimmed analysis—which excluded 2 of 111 (1.8%) natalizumab-treated patients, 6 of 104 (5.8%) fingolimod-treated patients, and 297 of 1,003 (29.6%) injectable DMT–treated PS outlier patients—also generated results consistent with the main analyses (eTables 5–7, links.lww.com/WNL/D451). The results of the ATT-weighted analyses were consistent with the primary analysis regardless of whether patients were weighted to be similar in baseline characteristics to those treated with natalizumab, fingolimod, or injectable DMTs (eTable 8). The results from the sensitivity analysis with a data cutoff of 2010 were consistent with those from the sensitivity analysis with a 2006 data cutoff, despite the reduction in number of patients treated with natalizumab (n = 91) or injectable DMTs (n = 724) in this period (eTables 9–11). Finally, the results of a sensitivity analysis in 83 of 111 (74.8%) natalizumab-treated patients, 62 of 104 (59.6%) fingolimod-treated patients, and 536 of 1,003 (53.4%) injectable DMT–treated patients with baseline MRI data were also consistent with the main primary and secondary analyses (eTables 12–14).

This study provides Class II evidence that patients with POMS treated with natalizumab had a lower risk of relapse than those with fingolimod.

Discussion

POMS is a rare disease, and patients aged younger than 18 years are excluded from most randomized MS trials. Because of the relative rarity of the disease and frequent off-label use, randomized trials require many centers and a long recruitment period and therefore are very expensive and difficult to conduct and complete.[31] In the absence of randomized clinical trial data, real-world evidence is increasingly used to investigate important clinical questions, including MS disease prognosis, predictors of treatment response and long-term outcomes, therapeutic effectiveness, and comparative effectiveness and safety of different DMTs.[32]

We conducted a 3-way IPTW analysis of real-world clinical data from the MSBase registry to compare the effectiveness of natalizumab, fingolimod, and injectable therapies (interferon-beta, glatiramer acetate) in patients with POMS. For the primary study end point, patients with POMS who initiated treatment with natalizumab or who switched to natalizumab from an injectable therapy showed a greater probability of remaining relapse-free than did those who initiated treatment with fingolimod or who switched to fingolimod from an injectable therapy. Patients treated with either natalizumab or fingolimod had a significantly greater probability of remaining relapse-free than did those treated with injectable therapies.

The adjusted secondary study outcomes were generally consistent with the primary outcome or with previous observations. Proportions of patients remaining on index therapy were significantly greater for patients treated with either natalizumab or fingolimod than with an injectable DMT. The time to index therapy discontinuation was essentially the same for natalizumab and fingolimod, and for all 3 groups, the most common reason for discontinuation was a lack of improvement.[33] Notably, the reason for discontinuation was not reported for approximately a third of discontinuing patients in each cohort suggesting further investigation may be warranted. However, the reason for discontinuation is not part of the minimum data set for the MSBase registry, which may

explain this amount of nonreporting. Concern over progressive multifocal leukoencephalopathy was not reported for any patient who discontinued natalizumab in this study, which contrasts with recent long-term real-world analyses of adult and pediatric users of natalizumab in whom this was the most common reason for discontinuation.[34,35]

Time to 24-week CDW was not significantly different among the 3 treatment groups. The lack of a differential treatment effect for natalizumab is consistent with previous studies of natalizumab in adult patients with relapsing-recurring MS in MSBase and is in part due to the relative rarity of CDW events in real-world observational studies of treated patients.[35]

Time to 24-week CDI was significantly lower in MSBase patients with pediatric MS treated with natalizumab or with fingolimod than in patients treated with an injectable DMT, consistent with previous clinical and real-world observations of patients with AOMS.[36,37] These observations are also consistent with evidence that natalizumab and fingolimod are effective anti-inflammatory agents, as assessed by reductions in relapse rates, in patients with POMS.[13]

The findings in the IPTW-adjusted patient populations were confirmed in multiple sensitivity analyses. Importantly, the analyses of PS–matched patients were generally consistent with the main analyses, as were the analyses of the trimmed IPTW-adjusted treatment groups.

There are limitations to real-world analyses. For rarer diseases such as POMS, randomized clinical trial data can be limited or unavailable and large multicenter networks and patient registries such as MSBase can provide access to more patients than could be enrolled in a randomized clinical trial. This real-world, retrospective cohort study of patients in the MSBase registry is subject to the limitations typical of real-world analyses and of registry-based studies specifically.[32] Aside from the nonrandomized design inherent to these studies, some residual indication bias can remain. Of particular relevance to this study, the results of MRI and their association with baseline disease activity and treatment choice are unknown for most of this population because MRI data are not part of the minimum data set within the MSBase registry. In addition, this study was unable to determine differences in outcomes between patients who received natalizumab or fingolimod as a first-line therapy vs those who were escalated from a previous injectable therapy because of the small number of treatment-naïve patients in these treatment groups.

When comparing patient cohorts from real-world data sources, patient groups must be balanced to address potential differences in baseline demographic or disease characteristics. Standard PS matching is not straightforward with 3 comparator groups because the target population after matching is not easily defined. Although a cutoff of <15% is commonly used in real-world, registry-based comparative effectiveness studies in MS,[38,39] we acknowledge that a small number of potential confounders in this study remained associated with standardized differences of >15% after adjustment. In addition, the algorithms used for matching generally need a larger sample size per treatment arm than was available to us. When weighting with IPTW, variations in baseline characteristics that predict an individual treatment are weighted so as to calculate PSs independent of treatment assignment.[40] Thus, each treatment group may be weighted to mirror baseline characteristics of the overall treated population. Furthermore, IPTW enables sensitivity analyses to compare weighting to baseline characteristics of the full analysis sample and weighting to baseline characteristic patterns present in each individual treatment group.

Although the 3 treatment groups appeared to be well balanced after IPTW, there is potential for residual bias because of unmeasured covariates. However, the consistent results obtained with the sensitivity analyses argue that such bias, if present, cannot account for the observed results. The similar results of the main and sensitivity analyses are evidence of the high internal validity of this study. However, it should also be noted that the trimmed analysis carried out to exclude PS outlier patients excluded a higher proportion of patients on injectables than patients treated with natalizumab or fingolimod, as the injectable subgroup had a higher proportion of patients at the extremes of the PS distribution and were thus overrepresented in the trim. It is not unreasonable to assume that the pediatric patients in this study who were treated with natalizumab or fingolimod have more severe disease than do those treated with injectable DMTs and might therefore be expected to have worse outcomes than those in the injectable group. This was not observed, however, suggesting that indication bias is significantly mitigated.

Overall, the results of this retrospective registry study are consistent with previous studies of natalizumab[13,22,24-28] and fingolimod in patients with POMS and therefore entirely expected.[21,41-45] Specifically, consistent results of the analyses of relapse risk in these 2 treatment groups suggests that natalizumab may be more effective than fingolimod on relapse outcomes. These effectiveness results are also generally consistent with comparative studies of natalizumab and fingolimod in adult patients with MS,[37,46-48] in concordance with the general agreement that pediatric-onset and adult-onset MS have similar underlying pathophysiology[14] and that outcomes for patients younger than 18 years are not fundamentally different than those for patients older than 18 years, although data supporting this point are limited.

It is highly likely that lower relapse rates would also be associated with lower brain and spinal cord lesion accumulation, with the potential for differential long-term benefits. Particularly, cognitive and productivity outcomes and time to secondary progressive MS are potentially improved with maximal control of the early inflammatory phase of relapsing-remitting MS. MSBase is planning to enhance its data collection for cognition and productivity outcomes in the future.

Larger cohorts with longer follow-up will be required to ultimately assess differential effects on protection from secondary progressive MS, as has been demonstrated for early use of high-efficacy therapies in AOMS.[49,50]

Our findings also demonstrate the usefulness of large MS registries and networks in general, and of the MSBase registry in particular, for comparative effectiveness studies of MS DMTs in rare patient populations that are difficult to study in a randomized setting. These results may also be helpful to health care providers and their patients in optimizing relapse control and potentially reducing the risk of persistent long-term disability in POMS. Interest in initiating therapy with high-efficacy DMTs such as natalizumab has grown over the past several years for patients with AOMS, and these data support a shift to initiating treatment with high-efficacy DMTs for patients with POMS as well.

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Appendix 1 Authors

Name	Location	Contribution
Tim Spelman, PhD, MBBS, BSc	MSBase Foundation, Melbourne, Australia; Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Gabrielle Simoneau, PhD, MSci, BSc	Biogen, Toronto, Ontario, Canada	Major role in the acquisition of data
Robert Hyde, PhD, BSc	Biogen, Baar, Switzerland	Major role in the acquisition of data

Appendix 1 *(continued)*

Name	Location	Contribution
Robert Kuhelj, PhD	Biogen, Baar, Switzerland	Major role in the acquisition of data
Raed Alroughani, MD	Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait	Major role in the acquisition of data
Serkan Ozakbas, MD	Dokuz Eylul University, Konak/Izmir, Turkey	Major role in the acquisition of data
Rana Karabudak, MD	Hacettepe University, Ankara, Turkey	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Bassem I. Yamout, MD	Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Lebanon	Major role in the acquisition of data
Samia J. Khoury, MD	Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Lebanon	Major role in the acquisition of data
Murat Terzi, MD	19 Mayis University, Samsun, Turkey	Major role in the acquisition of data
Cavit Boz, MD	KTU Medical Faculty Farabi Hospital, Trabzon, Turkey	Major role in the acquisition of data
Dana Horakova, MD, PhD	Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Czech Republic	Major role in the acquisition of data
Eva Kubala Havrdova, MD, PhD	Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Czech Republic	Major role in the acquisition of data
Bianca Weinstock-Guttman, MD	Department of Neurology, Buffalo General Medical Center, Buffalo, NY	Major role in the acquisition of data
Francesco Patti, MD	Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania, Italy	Major role in the acquisition of data
Ayse Altintas, MD	Department of Neurology, School of Medicine and Koc University Research Center for Translational Medicine (KUTTAM), Koc University, Istanbul, Turkey	Major role in the acquisition of data
Saloua Mrabet, MD	Department of Neurology and Clinical Investigation Center Neurosciences and Mental Health, Razi University Hospital, Tunis, Tunisia	Major role in the acquisition of data
Riadh Gouider, MD	Department of Neurology, Razi University Hospital, Tunis, Tunisia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jihad Inshasi, MD	Rashid Hospital, Dubai, United Arab Emirates	Major role in the acquisition of data
Vahid Shaygannejad, PhD	Isfahan University of Medical Sciences, Isfahan, Iran	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sara Eichau, MD, PhD	Department of Neurology, Hospital Universitario Virgen Macarena, Sevilla, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
W. Luke Ward, BCS	Ashfield MedComms, Middletown, CT	Drafting/revision of the manuscript for content, including medical writing for content
Helmut Butzkueven, MBBS, PhD	Department of Neuroscience, Central Clinical School, Monash University, Melbourne; Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Victoria, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/D453.

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